VOLUME 3 ISSUE 2: MAR-APR 2022

# INTERNATIONAL JOURNAL OF SCIENTIFIC ADVANCES

ISSN: 2708 - 7972

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IJSCIA

International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 3 | Issue: 2 | Mar - Apr 2022 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v3i2.22

# The Role of TGF-β in the Pathogenesis of Type 1 Diabetes Mellitus

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## ABSTRACT

Type 1 diabetes mellitus (T1DM) is a disease caused by dysregulation of the immune system with pancreatic cells as the targeted organ. The incidence of T1DM is increasing every year, with peak incidence at the age of 10-14 years. Genetic susceptibility and environmental exposure play important roles in immune system disorders. The failure of the tolerogenic process is one of the foremost processes causing pancreatic damage through the molecular mimicry process due to repeated infections both prenatally and postnatally. An increase in the expression of MHC class II and co-stimulator will trigger a shift in the balance of the shape of T cells, namely an increase in Th1 and Th7 cell differentiation, but a decrease in the number and function of Treg cells. TGF-β is a cytokine produced by Treg cells that functions to maintain tolerance in the human body. A decrease in TGF-β levels usually appears in the pre-diabetes stage. This review aims to elucidate the role of TGF- in the course of T1DM.

***Keywords:*** T1DM; molecular mimicry; Treg; TGF-β

## INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease that mostly affects children [1]. Immune system dysregulation such as failure of T cell-mediated tolerogenic processes, imbalance of pro-inflammatory and anti-inflammatory cytokine production, and formation of autoantibodies are responsible for pancreatic cell damage [2,3]. The prevalence of diabetes mellitus in a decade will increase by about 100 million people [1]. Transforming growth factor-β (TGF-β) is a pleiotropic regulatory protein that is both suppressive and proinflammatory to the immune response [4]. TGF-β contributes to maintaining an effective naive T cell population through regulation of proliferation, homeostasis, and diversity of T cell repertoire [5].

### T1DM Pathophysiology

The course of type 1 diabetes mellitus begins with genetic susceptibilities, such as polymorphisms in HLA, especially HLA-DR and HLA-DQ, and exposure to environmental agents. Recurrent viral infections both prenatally and postnatally, such as Coxsackievirus B1 infection and other enteroviruses will directly attack pancreatic cells specifically or through a molecular mimicry process which in turn involves the immune system thus damaging the pancreas [6-8]. The virus infects cells (not the pancreatic cells), then the peptide from the virus will be expressed by HLA class I which is recognized by CD8+ T cells. These viral proteins generally have the same amino acid sequence as pancreatic-cell proteins (e.g., proteins from Coxsackievirus B1 with glutamate decarboxylase) thereby triggering cytotoxic CD8+ T cells against infected cells and pancreatic cells. When virions undergo phagocytosis by macrophages, they are presented to CD4+ T cells via HLA class II, then B lymphocytes are activated and produce anti-viral antibodies and anti-pancreatic-cell autoantibodies [9].

This dysregulation of the immune system results in insulitis, a condition in which the remaining islet cells contain large nucleated cells, some degranulated cells, and chronic inflammatory infiltrate. The chronic inflammatory infiltrate contains predominantly CD8+ cells, the remainder includes CD4+ cells, B lymphocytes, macrophages, and natural killer (NK) cells. Meanwhile, the number of macrophages (CD68+), CD4+ T cells, B lymphocytes (CD20+) and plasma cells (CD138+) decreases. FOXP3+ cells (e.g. regulatory T cells) and NK cells are rarely found in the remaining pancreatic tissue [10]. A decrease in insulin secretion leading to impaired glucose tolerance or plasma glucose surge occurs several months before the onset. Damage to pancreatic cells reaches 90-95%, only a small amount of insulin and serum C-peptide levels remains, therefore exogenous insulin is given to maintain blood glucose levels [10].

### TGF-β on the Immune System

The name transforming growth factor-β (TGF-β) comes from its function, which is being able to transform and promote cell growth. The TGF-β family in humans consists of 33 types of proteins according to their coding genes. The most studied clusters of the TGF- family are the three isoforms of TGF-β, namely TGF-β1, -β2, and -β3. The TGF- family has diverse roles in regulating cell proliferation, cell differentiation, wound healing, controlling the immune system, and a key protein in pathological processes in vivo, such as connective tissue disorders, fibrosis, autoimmune diseases including T1DM and cancer. TGF-β polypeptide precursor structure is composed of three segments, namely amino-terminal signal peptide, carboxy-terminal TGF-β family monomer polypeptide, and latency-associated peptides (LAPs) [11].

Transforming growth factor-β (TGF-β) is a pleiotropic regulatory protein that is both suppressive and proinflammatory to the immune response [4]. Several studies have stated that TGF-β determines the type and magnitude of the immune response against microbes, besides that it also plays an important role in maintaining immune tolerance and homeostasis against self-antigens and innocuous antigens in the stable phase. It is TGF-β that contributes to maintaining an effective naive T cell population through the regulation of proliferation, homeostasis, and diversity of T cell repertoire. Sometimes an incomplete negative selection process in the thymus will result in some mature autoreactive T cells reaching the periphery. This autoreactive T cell in the periphery whose number is controlled by TGF-β is called peripheral tolerance [5].

The ability of TGF-β to regulate T cell proliferation depends on the status of T cell differentiation and the cumulative signaling pathway involved in cell activation, for example, TGF-β can inhibit the proliferation of naive CD4+ and CD8+ T cells but cannot inhibit the proliferation of active CD4+ and CD8+ T cells. The process of differentiation of CD4+ T cells into helper T cells 1 (Th1) and 2 (Th2) is inhibited by the TGF-β signal. Inhibition of differentiation of naive CD4+ T cells into Th1 cells is mediated by TGF-β expression through the activation of Smad2 and Smad3 transcription factors [4,12].

As previously mentioned, TGF-β is a pleiotropic cytokine that contributes to maintaining immune homeostasis through the proliferation, differentiation, activation, and function of effector cells of the immune system. Depending on the cytokine environment, TGF-β promotes the differentiation of peripheral CD4+ cells into anti-inflammatory Treg cells as well as Th17 cells and pro-inflammatory Th9 cells [12]. TGF-β also plays a role in promoting the development of Tfh (follicular helper T). TGF-β signaling induces the regulatory activity of naive Foxp3-expressing CD4+ T cells to pTreg. However, in conditions of infection when formations of many pro-inflammatory cytokines and strong costimulatory signals occur, inhibition of Foxp3 induction through TGF-β will occur. This suggests that pTreg cell differentiation is modulated by the microenvironment, with inflammatory conditions that favor effector cells over the production of Treg cells [5]. Another role of TGF-β in the body that has a negative impact is fibrosis which involves the deposition of extracellular matrix (such as collagen and fibronectin) via canonical and non-canonical signaling pathways. The canonical pathway is a TGF-β signaling pathway involving ALK5-Smad2/3, while the non-canonical pathway involves TGF-β/ALK1/SMAD1/5, MAP kinases (ERK, JNK, p38), PI3K/Akt, c-abl, JAK2 /STAT3, and Rho-associated coiled-coil containing protein kinases (ROCKs). Both pathways will work directly or in synergy with Smad protein to regulate protein expression. The active Smad protein will enter the nucleus and interact with DNA through binding to transcription factors (TF), co-activators (CA), and co-repressors (CR) regulating gene expression thereby increasing the production of extracellular matrix (ECM) including collagen, fibronectin, CTGF/ CCN2, and α-SMA) and decreasing MMP protein expression leading to fibrosis [13]. An increase in the amount of TGF-β for a long period will cause fibrosis in important organs such as the kidneys and eyes resulting in complications such as diabetic nephropathy and diabetic retinopathy [14,15].

**The Role of TGF-β in the Pathogenesis of T1DM**

Treg cells are activated in secondary lymphoid tissue-derived from naive FoxP3-expressing CD4+ T cells with the help of the TGF-β cytokine.

Treg cells, in carrying out their functions in regulating and suppressing both immune and inflammatory responses, produce IL-10 and TGF-β cytokines. Several peripheral tolerance mechanisms played by Treg cells include inhibiting T cell maturation by competing for binding to IL-2 cytokines by IL-2 receptors expressed by Treg cells. Treg cells secrete cytokines such as IL-10 and TGF-β which bind to receptors on active T cells and reduce the activity of these activated T cells. The function of APCs is also inhibited by Treg cells through inhibition of the CD80/86 co-stimulator on APCs which interacts with CTLA4 on Treg cells so that these APCs cannot stimulate T cells to become active. Treg cells are capable of destroying active T cells through perforin and granzyme secretion. Type 1 diabetes mellitus begins with the cells' failure of the tolerance process towards self-antigens. This process is initiated by polymorphisms in MHC class I and II in individuals, resulting in autoreactive CD4+ and CD8+ T cells that recognize pancreatic cell antigens too strongly. When APC introduces antigen to CD4+ T cells, IL-12 is formed which causes polarization, causing CD4+ T cells to become dominant Th1 and increasing the production of IFN-γ cytokine. On the other hand, the number of circulating Treg cells will decrease [16].

The following are some studies examining TGF-β in type 1 diabetes mellitus. A previous study by Azar et al. [17] in children with T1DM, T2DM, and controls who had normal plasma albumin levels succeeded in showing comparisons of TGF-β levels. The study showed something similar to this study, namely serum TGF-β levels would decrease significantly and the levels were lower in the T1DM group, especially those that have been diagnosed for more than 2 years [17]. A study by Ishigame et al., 2013 showed that the absence of a TGF-β signal on T cells in the thymus resulted in polarization, resulting in increased Th1 cell formation, whereas Th17 cells and Fox3+ Treg cells decreased [18].

Deletion of TGF-β signal on effector CD4+ T cells through TGFβRII ablation causes increased production of IFN-γ cytokines and polarization towards Th1, disruption of Treg cell homeostasis which manifests into T1DM (18). A similar result is shown in a study by Roohi et al. [19] claiming that TGF-β levels in the T1DM group were statistically lower than those in the control group. In a meta-analysis study, the result showed that the serum levels of TGF-β in the T1DM group were lower than in the control group [20]. A different result is shown by research by Zorena et al. [21] regarding the relationship between serum levels of TGF-β1 and the duration of illness of T1DM. The results showed that there was a statistically significant relationship between the duration of illness of T1DM and an increase in serum TGF-β1 levels. Patients with a duration of illness of more than 15 years who have elevated serum TGF-β1 1SD levels will have a 25% increased risk of microangiopathic complications.

A study of TGF-β as a diagnostic tool to predict the presence of diabetic retinopathy in T1DM stated that non-proliferative diabetic retinopathy (NPDR) patients had higher serum TGF-β levels than T1DM patients without diabetic retinopathy, while the T1DM group without diabetic retinopathy had higher TGF-β levels than the control group [15]. Factors that affect TGF-β levels include renin-angiotensin inhibitor agents, good glycemic control, normally controlled systolic blood pressure, statin consumption, nonsmoker, and a low protein diet. [22].

**TABLE 1:** Comparative literature on the role of tgf-β on t1dm pathogenesis

| Author, year | Research method | No. of study participants | Main result |
|---|---|---|---|
| Azar *et al.*, 2000 | Case-control | 26 T1DM patients<br>25 T2DM patients<br>27 children in the T1DM control group<br>15 children in the T2DM control group | • TGF-β will decrease significantly and the level is lower in the T1DM group than in the control group, and the highest in the T2DM group<br>• TGF-β serum levels will decrease significantly in the T1DM group, especially those that have been diagnosed for more than 2 years. |
| Roohi *et al.*, 2014 | Case-control | 24 T1DM patients<br>38 T2DM patients<br>30 control for T1DM<br>40 control for T2DM | • TGF-β levels in the T1DM group were statistically lower than controls with a median value (IQR) of 0(0) vs 184.52 (627.22) pg/mL, p=0.001. |
| Qiao *et al.*, 2016 | Meta-analysis | 1407 T1DM patients<br>1373 control | • TGF-β serum levels in the T1DM group were lower than in the control group |
| Zorena *et al.*, 2013 | Case-Control | 116 T1DM patients<br>19 healthy children as the control group | • Patients with a duration of illness of more than 15 years who have elevated serum TGF-β1 1SD levels will have a 25% increased risk of microangiopathic complications. A study of TGF-β as a diagnostic tool to predict the presence of diabetic retinopathy in T1DM stated that non-proliferative diabetic retinopathy (NPDR) patients had higher serum TGF-β levels than T1DM patients without diabetic retinopathy (1530 ± 465 pg/mL versus 758 ± 424 pg/mL, p= 0.003), while the T1DM group without diabetic retinopathy had higher TGF-β levels than the control group (758 ± 424 pg/mL versus 156 ± 49 pg/mL, p = 0.001). |

## CONCLUSION

Type 1 diabetes mellitus is an autoimmune disease that destroys pancreatic cells. This damage is mediated by the failure of tolerogenic processes that are influenced by TGF-β signals, namely by polarization differentiation of T cells towards Th1 and Th7 cells, while the number of Treg cells decreases. Failure to tolerate pancreatic autoantigens results in insulitis, a condition in which the remaining islet cells contain large nucleated cells, some degranulated cells, and chronic inflammatory infiltrate. The chronic inflammatory infiltrate contains predominantly CD8+ cells, the remainder includes CD4+ cells, B lymphocytes, macrophages, and natural killer (NK) cells. The islet cells remaining in the pancreas are usually less than 20%, therefore unable to keep insulin-dependent metabolism working properly, as occurs in T1DM.

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